REMARKS

Claims 1-61 are pending, claims 34-61 are new, and claims 1, 13, 18-20, 22 and 23 are amended. The new claims include one independent claim 34 and the subject matter of dependent claims 36-59 is nearly identical to that of dependent claims 2-22 as originally filed and claims 25, 28, and 31. New claims 35 and 60 are directed to subject matter amended out of claim 1 as it was originally filed. The amendments to claims 1, 13, 18-20, 22 and 23 improve the grammar of the claim language. New claims 34-61 and the claim amendments find basis in the claims as originally filed and throughout the specification (*see e.g.* page 7, lines 8-21). Thus, and the claim amendments and the new claims introduce no new matter and the claim amendments are non-narrowing.

Claim 13 was rejected under 35 U.S.C. § 112, second paragraph, as the term "type" was allegedly indefinite. This rejection is moot in view of the amendment to claim 13, which removes the term "type" from the claim. The claims also were rejected under 35 U.S.C. § 103 in view of Lang *et al.* (EP 487 774) alone and in combination with other documents. These obviousness rejections are respectfully traversed, and reasons for traversal are discussed separately below according to claim type: process, product by process, and product.

Process Claims 1-21 and 60

Pending claims 1-21 and 60 are directed to a thermal adhesion granulation process. This process is different than the methods described in Lang *et al.*, which discusses wet granulation, spray granulation, and spray drying processes. These latter processes are entirely different than the claimed process as they utilize greater amounts of solvent or water, they generate granules by a different mechanism, and they are carried out in an open system and not a closed system as specified by the claims.

One point of distinction between the wet granulation, spray granulation, and spray drying processes discussed in Lang *et al.* is that all of these processes involve a large amount of granulation fluid (*i.e.* water or organic solvent), whereas essentially dry processes are claimed.

In particular, the claimed processes specify that there is no more than a 20% initial moisture content in the mixture before heating. In contrast, the working examples of Lang *et al.* clearly teach that the granulation processes disclosed therein include much higher amounts of moisture. In Example I, which is a wet granulation process, the amount of water used was (0.49x5.0+2.9)/(5.0+0.67+2.9) = **62.4%**. In Example II, which is also wet granulation, the amount of water used was approximately (0.49x5)/(5+0.21+2) = 34.0% and the amount of ethanol used was approximately 2/(5+0.21+2) = 27.7%, for a combined initial moisture content of **61.7%**. In Example III, which is directed to fluidized bed granulation, the amount of water used was 4.5/(5+1.25+4.5) = **41.9%**. Thus, Lang *et al.* fails to disclose, teach, or suggest granulation techniques with mixtures having an initial moisture content of 20% or less.

The substantially dry thermal adhesion granulation process claimed offers several advantages over the wet granulation processes described in Lang *et al.* For example, a drying stage is either unnecessary or substantially reduced for the claimed methods, whereas the vast volumes of solvent or water required for the granulation methods discussed in Lang *et al.* require substantial post-granulation drying steps, thereby requiring drying equipment which further complicates the manufacturing process and significantly increasing the energy, cost, and production time of the overall process.

In addition, the mechanisms for carrying out granulation discussed in Lang *et al.* differ from the granulation mechanisms of the claimed methods. The wet granulation process discussed in Lang *et al.* is accomplished by forcing a wet, putty-like mixture through screens, sieves, choppers, and/or impellers to produce granules of desirable size. The fluidized bed and spray-drying granulation processes discussed in Lang *et al.* require that the mixture is sprayed. For example, in fluidized bed granulation, a binder solution is sprayed into powder suspended in an air stream, thereby causing the particles to coalesce through impaction. The air-suspended granules are dried as the solvent is evaporated. In contrast, the thermal adhesion granulation process claimed here does not require that the mixture is forced through a sieve or impeller assembly nor does it require that a binder solution is sprayed upon powder suspended in an air

stream. Rather, the thermal adhesion granulation process can be carried out by tumble rotation, as specified in claims 35 and 60. Thus, Lang *et al.* does not teach or suggest the mechanisms for granulation encompassed by the pending claims.

Certain process claims were rejected in view of the combination of Lang *et al.* and Kumar (U.S. Patent No. 6,117,451). Kumar does not cure the deficiencies of Lang *et al.* Specifically, Kumar discusses direct compression tabletting where lubricant is used but moisture and heating are not needed (*see e.g.* lines 7-36 of column 3 and claim 1 of Kumar). In contrast, moisture and heating are specified in the claimed thermal adhesion granulation process and lubricants are not required. Hence, Kumar fails to teach or suggest elements specified by the claims and does not add anything to Lang *et al.*

Furthermore, there was no motivation to combine Lang *et al.* with Kumar because each of the documents discussed absolutely distinct methods. For example, Lang *et al.* discussed methods requiring large amounts of solvent and Kumar discussed methods requiring no solvent at all. Thus, a person of ordinary skill in the art would not have been motivated to combine Lang *et al.* with Kumar.

The pending process claims also specify that mixing and heating steps in the thermal adhesion granulation process are carried out in a closed system. The Office alleges that these claims are rendered obvious by Lang *et al.* under the rationale that the document teaches a granulation method accomplished by utilizing a fluidized bed, which is characterized by the Office as a closed system. The Office provides no evidence that fluidized beds are closed systems, and it is the applicants understanding that fluidized beds are open systems as illustrated in the article attached as Exhibit B. This article shows that air entering inlet filters passes through the fluidized bed housing and then exits the top of the housing via a fan. Thus, the assertion that a fluidized bed is a closed system is based upon facts possibly within the personal knowledge of the examiner and such facts must be supported by an affidavit from the Examiner in accordance with 37 C.F.R. 1.104(d)(2). Accordingly, the applicants respectfully request an affidavit from the Examiner if the Office maintains the argument that a fluidized bed is a closed

system. In the absence of such evidence, the open fluidized bed systems are different then closed systems specified by claim 1 and its dependent claims.

Thus, Lang *et al.* does not result in the processes of claims 1-21 and 60 because the document fails to teach or suggest methods in which heating and mixing is carried out in a closed system. As Kumar (U.S. Patent No. 6,117,451), Ansel *et al.*, (1999), and Rodnick (Remington 1995) also failed to disclose processes in which material is heated and mixed in a closed system, they fail to cure this deficiency of Lang *et al.* Accordingly, neither Lang *et al.* or any of the cited combinations result in the processes of claims 1-21 and 61 and cannot support a *prima facie* case of obviousness.

New Process Claims 34-55

As described above, neither Lang *et al.* or any of the cited combinations can support a *prima facie* case of obviousness with respect to the newly claimed processes because they too are directed to the thermal adhesion granulation process and are limited to heating and mixing in a closed system. Furthermore, Lang *et al.* does not result in the new process claims because the documents alone and in combination fail to teach or suggest a thermal adhesion granulation process in which excipients and inactive ingredient are dry blended before water or a pharmaceutically acceptable organic solvent is added to the dry-blended mixture. Rather, Lang *et al.* is directed to wet granulation methods in which whetted excipients are individually combined with one another and then the resulting liquid mixture is subjected to sieving and/or drying methods. Thus, Lang *et al.* and the cited combinations do not result in the newly claimed processes and do not support a *prima facie* case for obviousness.

Product by Process Claims 22 and 56

The thermal adhesion granulation processes set forth in independent claims 1 and 34 result in a granulated product having different properties than those produced by the wet granulation processes disclosed in Lang *et al.* For example, the present application makes it

clear that the presence of excessive moisture in wet granulation processes can negatively affect ingredients in the tabletting formulation, which can result in reduced compressibility of certain excipients (*e.g.* page 3, lines 9-19). The enhanced compressibility of products of thermal adhesion granulation processes are evidenced by data set forth in the Examples section. Specifically, the tensile strength of tablets reported in Table 5 on page 19 of the specification are between 0.18 and 1.32 MPa, which are equivalent to 1.8×10^5 N/m^2 to 1.32×10^6 N/m^2 as there is a 1:1 conversion from Pa to N/m^2. Because the tensile strength of tablets disclosed in Lang *et al.* on page 4, lines 55-57, are 180-290 N, where the patentees most likely intended 180-290 N/m^2 as N/m^2 is a common unit for tensile strength, the tabletting compositions and products disclosed in the present application offered surprisingly advantageous tensile strengths that were significantly improved over the prior art.

Thus, the properties of products produced by the thermal adhesion granulation process differ from products produced by the wet granulation processes disclosed in Lang *et al.* or any other cited document, and therefore claims 22 and 56 are inventive over the cited documents. Accordingly, tablets, capsules, and pellets comprising such products, as set forth in claims 25, 28, 31, and 57-59 differ from those taught or suggested in the cited art.

Product Claims 23 and 24

Claim 23 is directed to a product containing PVP and DCPA. None of the cited documents teach or suggest this combination. While Kumar discusses DCPA as an agent that can improve blending and flow for dry mixing, such characteristics are not necessarily important for the wet granulation processes discussed in Lang *et al.* Because the dry mixing techniques discussed in Kumar are distinct from the wet granulation processes discussed in Lang *et al.*, there was no motivation for the person of ordinary skill in the art to combine the documents. As there was no motivation to combine Kumar with Lang *et al.* the cited combination cannot support a *prima facie* case for obviousness in connection with claim 23. Because claims 26, 29, and 32 depend from claim 23, they too are not obvious in view of the cited combination.

Claim 24 is directed to a tabletting formulation that was subjected to the disclosed thermal adhesion granulation process and led to a product having a significant tensile strength (*see e.g.* granule A' formulation in Table 3 on page 17). The cited documents alone or in combination did not teach this formulation because they did not envision (1) the thermal granulation process for which the claimed formulation is adapted, or (2) the products yielded by the process having improved compression characteristics. Also, there was no motivation to combine Lang *et al.* with Kumar, as explained above, and therefore the cited combination cannot support a *prima facie* case for obviousness in connection with claim 24. As claims 27, 30, and 33 depend from claim 24, they too are not obvious in view of the cited combination.

Method of Use Claim 61

Claim 61 is directed to a method of using DCPA as an anti-caking agent to generate a powder mixture having hygroscopic PVP. It is respectfully submitted that Kumar fails to teach methods of using DCPA as an anticaking agent. Rather, Kumar discusses methods of using DCPA as a binder or diluent, and does not disclose, teach, or suggest methods of using DCPA as an agent that can counter the hygroscopicity and clumping tendencies of PVP. Thus, Kumar does not anticipate claim 61, nor can it support a *prima facie* case for obviousness alone or in combination with the other cited documents.

CONCLUSIONS

It is respectfully requested that the Office withdraw the rejections of the claims under 35 U.S.C. § 112, second paragraph, as the claim amendments render the rejection moot. It also is respectfully requested that the Office withdraw the rejections under 35 U.S.C. § 103 as the cited documents alone and in combination fail to teach or suggest a thermal adhesion granulation process carried out in a closed system and because the claimed processes lead to products having different properties than those produced by wet granulation processes.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 205032001200.

Respectfully submitted,

Dated: March 3, 2003 By: _____

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